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Journal of Veterinary Cardiology

Spontaneous torsade de pointes and ventricular fibrillation in a dog during pacemaker implantation

--Manuscript Draft--

Manuscript Number:	JVC_2019_81R6
Article Type:	Case Report
Keywords:	canine; defibrillation; arrhythmia; third degree atrioventricular block; Anaesthesia
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	Yolanda Martinez Pereira
	Gudrun Schoeffmann
	Geoff Culshaw
Abstract:	This case report describes a case of spontaneous torsade de pointes in a dog during pacemaker implantation that degenerated into ventricular fibrillation. We discuss the key factors that may have precipitated this unusual complication, in which a pre-emptive resuscitation plan contributed to a successful outcome for the patient.
Response to Reviewers:	

Covering letter

Dear Editors and Reviewers,

First, thank you for your time reading and considering this case report for publication.

Torsade de pointes is an unusual ventricular arrhythmia seen in dogs. Pacemaker implantation carries several risks, both related to the procedure as well as to general anaesthesia. Premature ventricular complexes (VPCs) is the most common reported arrhythmia in dogs during general anaesthesia for this procedure, likely secondary to mechanical stimulation of the myocardium. In our experience, these are usually a few self-limited VPCs that do not generally degenerate into ventricular fibrillation.

This case report describes spontaneous torsade de pointes that degenerated into ventricular fibrillation in a dog. It also discusses the possible risk factors and on how they may have contributed for the clinical events.

We believe that this well documented case will bring attention to another possible life threatening complication during pacemaker implantation and highlights the importance of team work and preparation on the successful outcome of this particular clinical case.

I would like to thank in advance the editors and reviewers for their time and consideration.



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1st September 2020

Dear Drs Borgarelli and Fonfara,

Re: Manuscript JVC_2019_81.

Spontaneous torsade de pointes and ventricular fibrillation in a dog during pacemaker implantation.

Filipe L. Madruga, Yolanda Martinez Pereira, Gudrun Schoeffmann, Geoff J. Culshaw

Thank you for your reply, dated 24th August, 2020, together with the Reviewers' comments, regarding our manuscript.

We were delighted that Reviewer #2 considers our manuscript ready for publication. The authors wish to thank the Editors for considering this case report for publication, and the Reviewers for their time and constructive suggestions.

Yours sincerely,

Filipe Madruga, MRCVS

Torsade de pointes during pacemaker implantation

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Abstract

Torsade de pointes is an unusual complication seen in dogs during pacemaker implantation, although ventricular fibrillation has been previously reported. This case report describes torsade de pointes in a dog during pacemaker implantation that degenerated into ventricular fibrillation, and discusses the possible contributory factors. It also illustrates the relevance of a pre-emptive resuscitation plan and how this might have affected the outcome in the patient.

Keywords: arrhythmia, defibrillation, anaesthesia, third degree atrioventricular block, canine.

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Keywords: arrhythmia, defibrillation, anaesthesia, third degree atrioventricular block, canine.

Table of abbreviations

Abbreviation	Definition
AV	atrioventricular
BPM	beats per minute
ECG	electrocardiogram
IV	intravenous
PO	per os
SBP	systolic blood pressure
TdP	torsade de pointes
VF	ventricular fibrillation

CASE HISTORY

A 7.5 year old, neutered female, 33 kg Labrador retriever was presented following two weeks of exercise intolerance and three syncopal episodes. Third degree atrioventricular (AV) block had been diagnosed, and theophylline (15 mg/kg per os [PO] q 24 hr), terbutaline (0.15 mg/kg PO q 8 hr) and furosemide (1 mg/kg PO q 12 hr) were started prior to referral. On auscultation, the heart rate was 40 beats per minute (bpm) with strong, matching pulses. A grade 3/6 left apical systolic heart murmur and independent S4 heart sounds were audible. Systolic blood pressure (SBP), measured indirectly by the Doppler technique^a, was 150 mmHg. Electrocardiography confirmed third degree AV block. There were uncondacted P waves, at a rate of ~140 bpm, that were positive in leads I, II, III and aVF, and maximally negative in aVR, consistent with sinus origin [1]. They appeared to march through wide ventricular escape complexes of predominantly right bundle branch block morphology (0.07 s, ~40 bpm), and, occasionally, left bundle branch block morphology (0.09 s, Fig. 1). Echocardiography identified biventricular and biatrial dilation, despite normal systolic function [2] (Table 1). During subcostal assessment, there were hepatic venous congestion and a small amount of ascites. Bradycardia-induced right-sided congestive heart failure was diagnosed. Pre-anaesthetic bloodwork identified hypomagnesaemia (0.44 mmol/L, range 0.69 - 1.18 mmol/L) and moderately increased troponin-I (2.32 ng/mL, reference <0.05 ng/mL). Commercial plasma ELISAs for infectious agents (*Toxoplasma gondii*, *Borrelia burgdoferi*, *Dirofilaria immitis*, *Erlichia canis*, *Erlichia ewingii*, *Anaplasma phagocytophilum*, *Anaplasma platys*) associated with myocarditis were negative. Permanent pacemaker implantation was recommended.

Prior to general anaesthesia, pimobendan (0.15 mg/kg intravenous [IV]) was administered for inotropic support. A crash plan was discussed, including team role allocation and calculation of emergency drugs doses. Premedication consisted of pethidine (5 mg/kg intramuscularly) and acepromazine (0.01 mg/kg IV). Oxygen was continuously provided by mask. The skin was clipped over the left and right precordia, and radiotransparent, low-impedance pacing pads^b, with additional electrolyte gel on the contact side, were placed over the 5th-7th intercostal spaces [7]. To ensure good contact, adhesive dressing was wrapped over the pads and body wall. The electrode leads from the pads were connected to a defibrillator/monitor^c. Following skin preparation, the dog was transferred to theatre and placed in left lateral recumbency for temporary transvenous pacing. A 5 French bipolar pacing lead^d was inserted transcutaneously into the right lateral saphenous vein, and advanced under fluoroscopic guidance into the right ventricle. A single chamber external temporary pulse generator^e was used. Temporary pacing was started (VVI, 70 bpm) and general anaesthesia induced (propofol IV to effect) followed by maintenance with isoflurane in oxygen. The temporary pacing rate was increased to 120 bpm to maintain SBP at 125 mmHg. A steroid eluting, active fixation, 58 cm permanent endocardial lead^f was then inserted through a right jugular venotomy, and advanced under fluoroscopic guidance towards the apex of the right ventricle, aiming for a point of insertion within the distal interventricular septum. The permanent pulse generator and lead were connected together, temporary pacing was stopped, and pacing via the permanent lead (VVI, 120 bpm) was interrogated with a program system analyser^g. Lead impedance was 610 Ω . Loss of capture, using serial reductions in pacing voltage at 100 paced beats/min, occurred at 0.25 V. The sensitivity threshold, determined by serial increments in sensitivity at 30 endogenous ventricular escape beats per minute, was >12 mV. On

completion of sensitivity testing, the permanent pulse generator immediately resumed pacing at 120 bpm whereupon the patient's rhythm deteriorated acutely into torsade de pointes (TdP) followed by ventricular fibrillation (VF) (Figure 2). Cardiopulmonary resuscitation was instigated without delay. The surgeon performed thoracic compressions at approximately 70 compressions/minute. Within 20 seconds, the anaesthetist initiated a series of three direct current shocks (6 J/kg) delivered through the transcutaneous pacing patches, separated by short periods of several seconds to assess cardiac rhythm and re-instigate thoracic compressions. After the first shock, VF was still present. After the second shock, there was a brief period of ventricular tachycardia followed by TdP that degenerated into VF (Fig. 2). After the third shock, within 60 seconds of beginning resuscitation, the rhythm returned to third degree AV block with ventricular pacing at 120 bpm. At this point, an infusion of lidocaine (3 mg/kg/hr IV) was started. Blood pressure monitoring was not available after cardioversion because of electrical damage to the unit sustained during defibrillation. However, pulse quality felt subjectively strong and so pacemaker implantation was completed without further delay. Permanent lead placement was again confirmed on fluoroscopy. Lead impedance was 530 Ω and the capture threshold test (loss of capture still at 0.25 V), but not the sensitivity test, was repeated. The lead was secured at the venotomy site and the permanent pulse generator was secured within a subcutaneous pocket. Recovery from anaesthesia was unremarkable. No further spontaneous ventricular ectopy was observed, and lidocaine was gradually withdrawn over three hours. Prophylactic antibiotics with cefuroxime (20 mg/kg IV q 2 hr) was administered intra-operatively and continued with oral potentiated amoxicillin (20 mg/kg PO q 12 hr) post-operatively for 7 days. Analgesia included buprenorphine (0.02 mg/kg IV q 6 hr) and paracetamol (10 mg/kg IV q 12 hr), but was adjusted to

methadone (0.2 mg/kg IV) due to thoracic ecchymosis at the site of the pacing pads, possibly due to mild thermal skin injury from defibrillation [8]. Following 5 days in-hospital cage-rest, the patient was discharged with sotalol (1.2 mg/kg PO q 12 hr) and pimobendan (0.2 mg/kg PO q 12 hr) on restricted exercise.

The patient was assessed 1 month later. Syncope had not been observed and exercise tolerance had been gradually restored. Serum troponin-I had decreased to 0.11 ng/ml. No further tests were performed due to financial restraints. The pacemaker unit was functioning appropriately with no episodes of ventricular tachycardia recorded. Sensitivity was only assessed manually by gradually increasing the programmable sensitivity and shown to be >12mV. Pimobendan and sotalol were withdrawn.

DISCUSSION

Torsade de pointes, or multiform ventricular flutter, is a ventricular tachycardia characterised by polymorphic QRS complexes that twist around an imaginary baseline [9, 10]. Severely restricted cardiac output and potential deterioration into VF make this arrhythmia life-threatening [11]. When VF ensues, prompt electrical defibrillation is associated with higher survival rates [12].

This case report describes the successful management of TdP degenerating into VF. Ventricular fibrillation during pacemaker implantation has been described previously in one dog [13]. We believe that preparative plans in this patient positively influenced the outcome. Pre-placement of transcutaneous pacing/defibrillating pads, and a crash plan that included pre-calculated electrical energies, limited the delay to cardioversion.

123 The lead impedance and the low pacing threshold were unaffected by cardioversion,
124 suggesting that the permanent pacing lead was not damaged.

125 Ventricular ectopy is the most common arrhythmia during pacemaker implantation
126 [14]. In this dog, it could have resulted from a combination of electrical and mechanical
127 stimulation of the myocardium, which elevated troponin I suggested was inflamed.
128 What is not clear is why ventricular ectopy should degenerate so acutely into life-
129 threatening TdP and VF in this case.

130 Spontaneous TdP and VF are associated with prolongation of cardiac repolarisation,
131 because, as the period of repolarisation increases, inward depolarising currents (early
132 afterdepolarisations) and intra-myocardial electrical heterogeneity are more likely to
133 occur [15]. Prolonged repolarisation during sinus rhythm can manifest as a long QT
134 interval on the surface ECG. This is observed in people with inherited Long-QT1 and
135 Long-QT2, in which dysfunctional myocardial repolarising I_{Ks} and I_{Kr} channels
136 generate early afterdepolarisations, re-entry and TdP, thus increasing the risk of
137 sudden death [15, 16].

138 Similar phenomena may occur during prolonged cardiac repolarisation in veterinary
139 patients. For example, I_{Ks} potassium channel abnormalities have been implicated in
140 the development of early afterdepolarisations and lethal tachyarrhythmias in German
141 shepherd dogs [17]. The dog in this case was pacemaker dependent, and so cardiac
142 polarisation was prolonged as a consequence of ventricular paced beats and/or
143 endogenous escape beats that generated wide complexes on the ECG. Indeed, in
144 experimental canine models of TdP, chronic, permanent third degree AV block is
145 utilised to generate prolonged cardiac repolarisation from ventricular escape beats
146 [18]. Once repolarisation is prolonged, TdP can then be induced through additional

147 pharmacological or electrical stimulation. One experimental protocol includes the use
148 of sotalol, which prolongs repolarisation further by inhibiting I_{Kr} . Therefore, the use of
149 sotalol post-operatively in our case, which by this stage had already experienced TdP,
150 may actually have been contra-indicated [19].

151 Additional pharmacological influences could have come from two different
152 sympathomimetic drugs, which were used simultaneously in this case. Beta 2
153 agonists, such as terbutaline, can prolong QT intervals and promote tachyarrhythmias,
154 including VF [20, 21]. This occurs especially when combined with methylxanthines
155 [22], such as theophylline, which inhibit phosphodiesterase III. Both agents increase
156 intracellular calcium, promoting delayed afterdepolarisations, and triggering TdP.
157 Such an effect has not been reported previously in dogs in a clinical setting; however,
158 in our experience, it is unusual for a patient to receive both drugs simultaneously
159 immediately prior to pacemaker implantation. Additional anti-phosphodiesterase III
160 activity from pimobendan, administered before inducing anaesthesia, may also have
161 been deleterious.

162 Although pacemakers are routinely placed in dogs under general anaesthesia, the
163 potential contribution of anaesthetic agents to TdP cannot be ignored. The
164 premedicant used in this case, acepromazine, is a phenothiazine sedative that is often
165 selected because it reduces myocardial sensitivity to catecholamines, thus reducing
166 calcium overload. However, it also prolongs cardiac repolarisation in dogs by inhibiting
167 potassium channels [23]. Even the maintenance agent that was used, isoflurane,
168 prolongs QT intervals in dogs [24, 25], promoting the development of TdP [26]. We
169 also speculate that, pre-anaesthesia correction of the mild hypomagnesaemia could
170 have been beneficial in this dog. Hypomagnesaemia is associated with TdP in people
171 [27], and resolution of TdP in a dog following administration of magnesium sulphate

has been reported [28]. No other electrolyte abnormalities were detected in our case.

Hypokalaemia reduces the ability to repolarise effectively, but, although this dog received a potassium losing diuretic, furosemide, for congestive heart failure, serum potassium levels remained within the reference range.

As well as pharmacological manipulation, electrical stimulation of the heart is a likely contributory factor to the development of TdP and VF. Torsade de pointes developed immediately after the termination of permanent lead sensitivity testing, in which the program system analyser lowered the pacing rate to 30 bpm, using long cycle lengths to encourage an endogenous ventricular escape rhythm. On termination of the sensitivity test, the programmed pacing rate of 120 bpm was immediately restored. This sequence of events has similarities to the protocol for TdP induction in experimental third degree AV block in dogs [18]. In these dogs, short and long cycle lengths and prolonged pacing followed by an extrastimulus (8+1) successfully induce TdP. This pro-arrhythmic effect of pacing has also been described in people, where short-long-short pacing facilitated ventricular tachycardia/VF [29] and VF [30].

Although it is not possible to determine the effect of any single agent or factor on the development of TdP and VF in this case, we believe it is reasonable to speculate on a cumulative effect of third degree AV block, myocarditis, anaesthetic agents, combination sympathomimetics, hypomagnesaemia and short-long-short cycle length pacing. This case report also illustrates the importance of preparation for defibrillation prior to pacemaker implantation, and has implications for sensitivity testing during the procedure. Most dogs with third degree AV block have wide ventricular escape complexes on ECG, suggestive of prolonged cardiac repolarisation that could increase their susceptibility to TdP and VF, especially if they have received sympathomimetics.

Footnotes

^a Model 811-B Doppler Ultrasonic Flow Detector, Parks Medical Inc., Aloha, Oregon,

United States of America

^b RTS (Radiotransparent) Pediatric EDGE System Electrodes with QUIK-COMBO

Connector, Physio – Control Inc., Redmond, Washington, United States of America

^c LIFEPAK 20e defibrillator/monitor, Physio – Control Inc., Redmond, Washington,

United States of America

^d Radifocus® Introducer II Standard Kit, Terumo, Leuven, Belgium

^e APC® External Pulse Generator type E4162, Implants Division of Devices Ltd.,

Hatfield, United Kingdom

^f Vitatron Crystalline ActFix, Vitatron, Arnhem, The Netherland

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Legend of figures

Figure 1 – Electrocardiogram of the patient recorded on admission, showing 3rd degree atrioventricular block (paper speed 50 mm/s, sensitivity 5 mm/V), heart rate = 39 beats per minute, showing non-conducted P waves (A) dissociated from ventricular escape complexes of right bundle branch block morphology (B, 0.07 s duration), and left bundle branch block morphology (C, 0.09 s duration). Coupling intervals between complexes B and C were not fixed during prolonged recording, suggesting that they arose from independent escape foci.

Figure 2 – Electrocardiogram demonstrates torsade de pointes (TdP) and ventricular fibrillation (VF). This print was obtained from the defibrillator unit, and acquired before the first direct current shock. The first period of TdP prior to VF was not recorded. Ventricular fibrillation (A) is unresponsive to shock 1, converts to a polymorphic, rapid ventricular tachycardia (B) after shock 2, before degenerating into TdP (C), and then VF (D). Shock 3 restores paced rhythm (E) at 120 beats per minute.

Figure 1

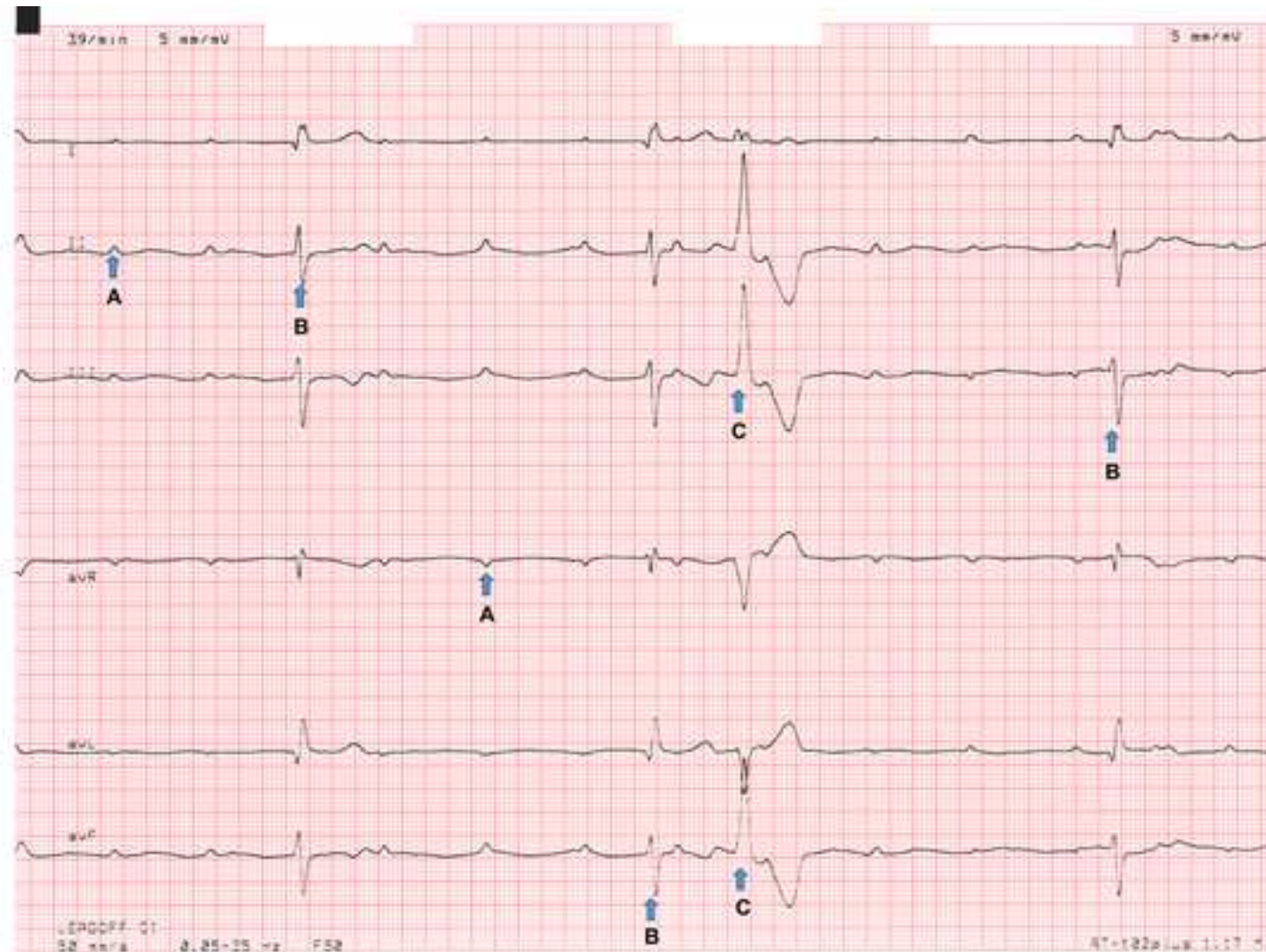


Figure 2

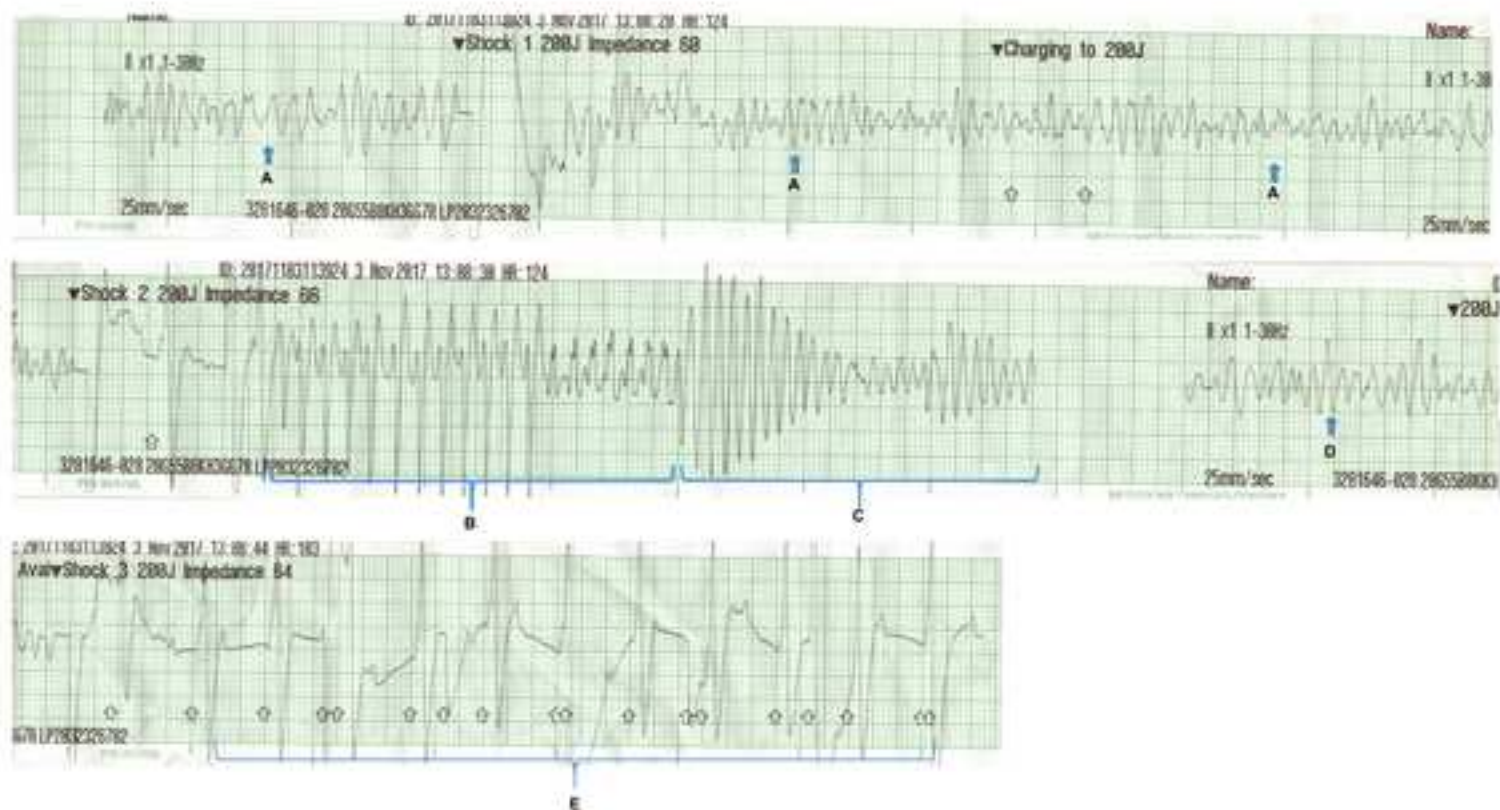


Table 1 – Echocardiography results of the patient on admission

Parameter assessed	Result	Range [reference]
LVIDdN (mm)	2.081	1.270 – 1.850 mm [1]
LVIDsN (mm)	0.924	0.710 – 1.260 mm [1]
FS (%)	52.2	25.3 – 49.9 % [2]
EDVI (mL/m ²)	104.0	32.9 – 69.1 mL/m ² [3]
ESVI (mL/m ²)	14.2	9.5 – 25.4 mL/m ² [3]
EF (%)	86.3	54.4 – 75.7 % [3]
LAD (mm)	31.6	25.0 – 36.0 mm [4]
Aortic Velocity (m/s)	3.70	0.92 – 1.88 m/s [5]
Pulmonary Velocity (m/s)	1.43	0.50 – 1.50 m/s [5]

EDVI: End-diastolic volume index; EF: Ejection fraction; ESVI: End-systolic volume index; FS: Fractional shortening; LAD: Left atrial diameter; LVIDdN: Normalised left ventricular internal dimension at end-diastole; LVIDsN: Normalised left ventricular internal dimension at end-systole.

Table of abbreviations

Abbreviation	Definition
AV	atrioventricular
BPM	beats per minute
ECG	electrocardiogram
IV	intravenous
PO	per os
SBP	systolic blood pressure
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Journal of Veterinary Cardiology

The following information is required for submission:

Author contribution

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Please specify the contribution of **each author** to the paper, e.g. study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways, should be listed as contributors.

Geoff Culshaw – Significant contribution interpretation of data and critical analysis. Major contribution regarding critical revision. Final approval of the version to be published.

Yolanda Martinez-Pereira – Significant critical revision.

Gudrun Schoeffmann – Critical revision

As **Corresponding Author** I hereby confirm that all listed authors in the submission meet these Criteria.

Corresponding author: Filipe Lalanda Madruga

Please add signature here:



Date: 28th April 2020